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e 662, TRADEMARKSCAN(R) - Austria
***File 669, TRADEMARKSCAN(R) - Japan
***File 678, TRADEMARKSCAN(R) - Norway
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FILES REMOVED
***File 301, CHEMNAME - please use File 398 ChemSearch
***File 388, PEDS: Defense Program Summaries
***File 588, DMS-FI Contract Awards

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File   1:ERIC 1965-2009/May
       (c) format only 2009 Dialog

      Set  Items  Description
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Cost is in DialUnits
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             $0.59    0.164 DialUnits File1
     $0.59  Estimated cost File1
     $0.59  Estimated cost this search
     $0.59  Estimated total session cost   0.164 DialUnits

File 410:The Chronolog 2009
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      Set  Items  Description
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HILIGHT set on as ''
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       29jun09 12:01:38 User208760 Session D3077.2
             $0.00    0.115 DialUnits File410
     $0.00  Estimated cost File410
     $0.02  TELNET
     $0.02  Estimated cost this search
     $0.61  Estimated total session cost   0.279 DialUnits

SYSTEM:OS  - DIALOG OneSearch
  File   5:Biosis Previews(R) 1926-2009/Jun W3
         (c) 2009 The Thomson Corporation
  File  73:EMBASE 1974-2009/Jun 25
         (c) 2009 Elsevier B.V.
  File 155:MEDLINE(R) 1950-2009/Jun 26
         (c) format only 2009 Dialog
  File 399:CA SEARCH(R) 1967-2009/UD=15101
         (c) 2009 American Chemical Society
*File 399: Use is subject to the terms of your user/customer agreement.
IPCR/8 classification codes now searchable as IC=. See HELP NEWSIPCR.

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Ref   Items  Index-term
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E3        0 *AU=JUNE CARL ?
E4      230  AU=JUNE CARL H
E5        3  AU=JUNE CARLE H
E6        1  AU=JUNE CHANG
E7        1  AU=JUNE CHANG SUNG
E8        2  AU=JUNE CHIA-PING
E9        1  AU=JUNE CINDY
E10       2  AU=JUNE D
E11       1  AU=JUNE D B
E12       7  AU=JUNE D S

          Enter P or PAGE for more
? s e3-e4
             0  AU=JUNE CARL ?
           230  AU=JUNE CARL H
      S1   230  E3-E4
? s s1 and (cd3 or okt3) and (cd28)
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         96835  CD3
         10854  OKT3
         27181  CD28
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? rd s4
      S5    9  RD S4  (unique items)
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 5/3/1     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
(c) 2009 The Thomson Corporation. All rts. reserv.

13885939   BIOSIS NO.: 199799519999
Telomere length, telomerase activity, and replicative potential in HIV
  infection: Analysis of CD4+ and CD8+ T cells from HIV-discordant
  monozygotic twins
AUTHOR: Palmer Larry D; Weng Nan-Ping; Levine Bruce L; June Carl H; Lane H
  Clifford; Hodes Richard J (Reprint)
AUTHOR ADDRESS: National Inst. Health, 9000 Rockville Pike, Bethesda, MD
  20892, USA**USA
JOURNAL: Journal of Experimental Medicine  185 (7): p1381-1386 1997
1997
ISSN: 0022-1007
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English


 5/3/2     (Item 2 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
(c) 2009 The Thomson Corporation. All rts. reserv.

13884652   BIOSIS NO.: 199799518712
```

Differential regulation of HIV-1 fusion cofactor expression by CD28
costimulation of CD4+ T cells
AUTHOR: Carroll Richard G; Riley James L; Levine Bruce L; Feng Yu; Kaushal
Sumesh; Ritchey David W; Bernstein Wendy; Weislow Owen S; Brown Charles R
; Berger Edward A; June Carl H (Reprint); St Louis Daniel C
AUTHOR ADDRESS: Jackson Found. Advancement of Military Med., Rockville, MD
20850, USA**USA
JOURNAL: Science (Washington D C) 276 (5310): p273-276 1997 1997
ISSN: 0036-8075
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

5/3/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13455382 BIOSIS NO.: 199699089442
Antiviral effect and ex vivo CD4+ T cell proliferation in HIV-positive
patients as a result of CD28 costimulation
AUTHOR: Levine Bruce L; Mosca Joseph D; Riley James L; Carroll Richard G;
Vahey Maryanne T; Jagodzinski Linda L; Wagner Kenneth F; Mayers Douglas L
; Burke Donald S; Weislow Owen S; Louis Daniel C S; June Carl H
(Reprint)
AUTHOR ADDRESS: Naval Med. Res. Inst., Bethesda, MD 20889, USA**USA
JOURNAL: Science (Washington D C) 272 (5270): p1939-1943 1996 1996
ISSN: 0036-8075
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

5/3/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13453819 BIOSIS NO.: 199699087879
Regulated expression of telomerase activity in human T lymphocyte
development and activation
AUTHOR: Weng Nan-Ping (Reprint); Levine Bruce L; June Carl H; Hodes
Richard J
AUTHOR ADDRESS: Experimental Immunol., Branch, Natl. Cancer Inst., Natl.
Inst. Health, Build. 10, Room 4-B17, Bethesda, MD 20892, USA**USA
JOURNAL: Journal of Experimental Medicine 183 (6): p2471-2479 1996
1996
ISSN: 0022-1007
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

5/3/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12933991 BIOSIS NO.: 199598401824
Both CD28 ligands CD80 (B7-1) and CD86 (B7-2) activate
phosphatidylinositol 3-kinase, and wortmannin reveals heterogeneity in
the regulation of T cell IL-2 secretion
AUTHOR: Ueda Yuji (Reprint); Levine Bruce L; Huang Mark L; Freeman Gordon J

; Nadler Lee M; June Carl H; Ward Stephen G
AUTHOR ADDRESS: Immune Cell Biol. Program, Naval Med. Res. Inst., Bethesda, MD 20889, USA**USA
JOURNAL: International Immunology 7 (6): p957-966 1995 1995
ISSN: 0953-8178
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

5/3/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12933989 BIOSIS NO.: 199598401822
CD28 ligands CD80 (B7-1) and CD86 (B7-2) induce long-term autocrine growth of CD4+ T cells and induced similar patterns of cytokine secretion in vitro
AUTHOR: Levine Bruce L; Ueda Yuji; Craighead Nancy; Huang Mark L; June Carl H (Reprint)
AUTHOR ADDRESS: Immune Cell Biol. Program, Naval Med. Res. Inst., Bethesda, MD 20889, USA**USA
JOURNAL: International Immunology 7 (6): p891-904 1995 1995
ISSN: 0953-8178
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

5/3/7 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12713229 BIOSIS NO.: 199598181062
CD28 activation promotes Th2 subset differentiation by human CD4+ cells
AUTHOR: King Christopher L (Reprint); Stupi Robert L; Craighead Nancy; June Carl H; Thyphronitis George
AUTHOR ADDRESS: Div. Geographic Med., Case Western Reserve Univ., 2109 Adelbert Rd., Cleveland, OH 44106-4983, USA**USA
JOURNAL: European Journal of Immunology 25 (2): p587-595 1995 1995
ISSN: 0014-2980
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

5/3/8 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12672161 BIOSIS NO.: 199598139994
Distinct signal transduction in mouse CD4+ and CD8+ splenic T cells after CD28 receptor ligation
AUTHOR: Abe Ryo (Reprint); Vandenberghe Peter; Craighead Nancy; Smoot Douglas S; Lee Kelvin P; June Carl H
AUTHOR ADDRESS: Immune Cell Biol. Program, Naval Med. Research Inst., Tissue Bank, Build. 1, Room 159, 8901 Wisconsin Ave., Code 0613, Bethesda, MD 20889, USA**USA
JOURNAL: Journal of Immunology 154 (3): p985-997 1995 1995
ISSN: 0022-1767

DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

5/3/9 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11984278 BIOSIS NO.: 199497005563
Rapid activation of c-Raf-1 after stimulation of the T-cell receptor or the muscarinic receptor type 1 in resting T cells
AUTHOR: Siegel Jeffrey N (Reprint); June Carl H; Yamada Hidehiro; Rapp Ulf R; Samelson Lawerence E
AUTHOR ADDRESS: NMRI/ICBP, Mail Stop 6, Bethesda, MD 20889-5607, USA**USA
JOURNAL: Journal of Immunology 151 (8): p4116-4127 1993 1993
ISSN: 0022-1767
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
? s s5 and (same)
9 S5
2400213 SAME
S6 0 S5 AND (SAME)
? t s5/7/all

5/7/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13885939 BIOSIS NO.: 199799519999
Telomere length, telomerase activity, and replicative potential in HIV infection: Analysis of CD4+ and CD8+ T cells from HIV-discordant monozygotic twins
AUTHOR: Palmer Larry D; Weng Nan-Ping; Levine Bruce L; June Carl H; Lane H Clifford; Hodes Richard J (Reprint)
AUTHOR ADDRESS: National Inst. Health, 9000 Rockville Pike, Bethesda, MD 20892, USA**USA
JOURNAL: Journal of Experimental Medicine 185 (7): p1381-1386 1997 1997
ISSN: 0022-1007
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: To address the possible role of replicative senescence in human immunodeficiency virus (HIV) infection, telomere length, telomerase activity, and in vitro replicative capacity were assessed in peripheral blood T cells from HIV+ and HIV- donors. Genetic and age-specific effects on these parameters were controlled by studying HIV-discordant pairs of monozygotic twins. Telomere terminal restriction fragment (TRF) lengths from CD4+ T cells of HIV+ donors were significantly greater than those from HIV- twins. In contrast, telomere lengths in CD8+ T cells from HIV+ donors were shorter than in HIV- donors. The in vitro replicative capacity of CD4+ cells from HIV+ donors was equivalent to that of HIV- donors in response to stimulation through T cell receptor CD3 and CD28. Little or no telomerase activity was detected in freshly isolated CD4+ or CD8+ lymphocytes from HIV+ or HIV- donors, but was induced by in vitro stimulation of both HIV+ and HIV- donor cells. These results suggest that HIV infection is associated with alterations in the population dynamics of both CD4+ and CD8+ T cells, but fail to provide evidence for clonal

exhaustion or replicative senescence as a mechanism underlying the decline in CD4+ T cells of HIV-infected donors.

5/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13884652 BIOSIS NO.: 199799518712
Differential regulation of HIV-1 fusion cofactor expression by CD28 costimulation of CD4+ T cells
AUTHOR: Carroll Richard G; Riley James L; Levine Bruce L; Feng Yu; Kaushal Sumesh; Ritchey David W; Bernstein Wendy; Weislow Owen S; Brown Charles R ; Berger Edward A; June Carl H (Reprint); St Louis Daniel C
AUTHOR ADDRESS: Jackson Found. Advancement of Military Med., Rockville, MD 20850, USA**USA
JOURNAL: Science (Washington D C) 276 (5310): p273-276 1997 1997
ISSN: 0036-8075
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Activation of CD4+ T lymphocytes from human immunodeficiency virus-type 1 (HIV 1)-infected donors with immobilized antibodies to ***CD3*** and ***CD28*** induces a virus resistant state. This effect is specific for macrophage-tropic HIV-1. Transcripts encoding CXCR4/Fusin, the fusion cofactor used by T cell line-tropic isolates, were abundant in CD3/CD28-stimulated cells, but transcripts encoding CCR5, the fusion cofactor used by macrophage-tropic viruses, were not detectable. Thus, CD3/CD28 costimulation induces an HIV-1-resistant phenotype similar to that seen in some highly exposed and HIV-uninfected individuals.

5/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13455382 BIOSIS NO.: 199699089442
Antiviral effect and ex vivo CD4+ T cell proliferation in HIV-positive patients as a result of CD28 costimulation
AUTHOR: Levine Bruce L; Mosca Joseph D; Riley James L; Carroll Richard G; Vahey Maryanne T; Jagodzinski Linda L; Wagner Kenneth F; Mayers Douglas L ; Burke Donald S; Weislow Owen S; Louis Daniel C S; June Carl H (Reprint)
AUTHOR ADDRESS: Naval Med. Res. Inst., Bethesda, MD 20889, USA**USA
JOURNAL: Science (Washington D C) 272 (5270): p1939-1943 1996 1996
ISSN: 0036-8075
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Because stimulation of CD4+ lymphocytes leads to activation of human immunodeficiency virus-type 1 (HIV-1) replication, viral spread, and cell death, adoptive CD4+ T cell therapy has not been possible. When antigen and CD28 receptors on cultured T cells were stimulated by monoclonal antibodies (mAbs) to CD3 and CD28 that had been immobilized, there was an increase in the number of polyclonal CD4+ T cells from HIV-infected donors. Activated cells predominantly secreted cytokines associated with T helper cell type 1 function. The HIV-1 viral load declined in the absence of antiretroviral agents. Moreover,

CD28 stimulation of CD4+ T cells from uninfected donors rendered these cells highly resistant to HIV-1 infection. Immobilization of CD28 mAb was crucial to the development of HIV resistance, as cells stimulated with soluble CD28 mAb were highly susceptible to HIV infection. The ***CD28*** -mediated antiviral effect occurred early in the viral life cycle, before HIV-1 DNA integration. These data may facilitate immune reconstitution and gene therapy approaches in persons with HIV infection.

5/7/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13453819 BIOSIS NO.: 199699087879
Regulated expression of telomerase activity in human T lymphocyte development and activation
AUTHOR: Weng Nan-Ping (Reprint); Levine Bruce L; June Carl H; Hodes Richard J
AUTHOR ADDRESS: Experimental Immunol., Branch, Natl. Cancer Inst., Natl. Inst. Health, Build. 10, Room 4-B17, Bethesda, MD 20892, USA**USA
JOURNAL: Journal of Experimental Medicine 183 (6): p2471-2479 1996 1996
ISSN: 0022-1007
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Telomerase, a ribonucleoprotein that is capable of synthesizing telomeric repeats, is expressed in germline and malignant cells, and is absent in most normal human somatic cells. The selective expression of telomerase has thus been proposed to be a basis for the immortality of the germline and of malignant cells. In the present study, telomerase activity was analyzed in normal human T lymphocytes. It was found that telomerase is expressed at a high level in thymocyte subpopulations, at an intermediate level in tonsil T lymphocytes, and at a low to undetectable level in peripheral blood T lymphocytes. Moreover, telomerase activity is highly inducible in peripheral T lymphocytes by activation through CD3 with or without CD28 co-stimulation, or by stimulation with phorbol myristate acetate (PMA)/ionomycin. The induction of telomerase by anti-CD3 plus anti-CD28 (anti-CD3/CD28) stimulation required RNA and protein synthesis, and was blocked by herbimycin A, an inhibitor of Src protein tyrosine kinases. The immuno-suppressive drug cyclosporin A selectively inhibited telomerase induction by PMA/ionomycin and by anti-CD3, but not by anti- ***CD3*** / ***CD28*** . Although telomerase activity in peripheral T lymphocytes was activation dependent and correlated with cell proliferation, it was not cell cycle phase restricted. These results indicate that the expression of telomerase in normal human T lymphocytes is both developmentally regulated and activation induced. Telomerase may thus play a permissive role in T cell development and in determining the capacity of lymphoid cells for cell division and clonal expansion.

5/7/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12933991 BIOSIS NO.: 199598401824
Both CD28 ligands CD80 (B7-1) and CD86 (B7-2) activate phosphatidylinositol 3-kinase, and wortmannin reveals heterogeneity in

the regulation of T cell IL-2 secretion
AUTHOR: Ueda Yuji (Reprint); Levine Bruce L; Huang Mark L; Freeman Gordon J ; Nadler Lee M; June Carl H; Ward Stephen G
AUTHOR ADDRESS: Immune Cell Biol. Program, Naval Med. Res. Inst., Bethesda, MD 20889, USA**USA
JOURNAL: International Immunology 7 (6): p957-966 1995 1995
ISSN: 0953-8178
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: In this report, the co-stimulatory signals provided by CD80 (B7-1) or CD86 (B7-2) were compared to ***CD28*** ligation by mAb. We demonstrate that while both anti-CD3 and anti-CD28 antibodies induced activation of phosphoinositide (PI) 3-kinase, the kinetics of activation differed. Anti- ***CD28*** produced a sustained activation of PI 3-kinase while anti- ***CD3*** induced activation was transient. Both B7-1 and B7-2 could induce prolonged activation of PI 3-kinase. The co-stimulatory effects of B7-1 and B7-2 were dependent on CD28 cross-linking, based on complete inhibition of PI 3-kinase activation by ***CD28*** antibody Fab fragments. While Jurkat T cells co-stimulated with anti-CD3 and B7-1 or B7-2 secreted high levels of IL-2, there were distinct effects of anti-CD28 mAb and B7-1 or B7-2 on IL-2 secretion in conjunction with protein kinase C activation. To assess functional effects of CD28 ligation, pharmacologic inhibitors of PI 3-kinase were evaluated. In Jurkat cells, efficient inhibition of PI 3-kinase activation after B7-2 stimulation was achieved using wortmannin; however, we observed a surprising increase in IL-2 secretion after B7 or anti- ***CD28*** stimulation. The effect of wortmannin was concentration dependent. Moreover, the effect was specific for receptor-mediated activation as wortmannin did not enhance phorbol ester plus ionomycin-induced IL-2 secretion. Another inhibitor of PI 3-kinase, LY294002, also resulted in augmentation of anti-CD28-induced IL-2 secretion by Jurkat cells. The effects of wortmannin on IL-2 secretion were also examined in primary T cells. In marked contrast, wortmannin resulted in a potent inhibition of anti-CD3 plus B7-1 or anti-CD28-induced IL-2 secretion while phorbol ester plus ionomycin-induced IL-2 secretion was wortmannin resistant. Together these observations demonstrate that signal transduction by both B7-1 and B7-2 involves PI 3-kinase, and that PI 3-kinase or other wortmannin-sensitive targets are important for IL-2 secretion. Finally, treatment of Jurkat cells with PI 3-kinase inhibitors alone was sufficient to induce low levels of IL-2 secretion. This is consistent with the notion that a wortmannin-sensitive target such as PI 3-kinase may down-regulate IL-2 secretion in Jurkat cells.

5/7/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12933989 BIOSIS NO.: 199598401822
CD28 ligands CD80 (B7-1) and CD86 (B7-2) induce long-term autocrine growth of CD4+ T cells and induced similar patterns of cytokine secretion in vitro
AUTHOR: Levine Bruce L; Ueda Yuji; Craighead Nancy; Huang Mark L; June Carl H (Reprint)
AUTHOR ADDRESS: Immune Cell Biol. Program, Naval Med. Res. Inst., Bethesda, MD 20889, USA**USA
JOURNAL: International Immunology 7 (6): p891-904 1995 1995
ISSN: 0953-8178

DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The interaction of CD28 and its ligands is critical for antigen-induced T cell activation. Recent studies have demonstrated the existence of at least two members of the B7 receptor family. In this report, the co-stimulatory signals provided by CD80 (B7-1) or CD86 (B7-2) were compared to ***CD28*** ligation by mAb. We demonstrate that the kinetics of induction of T cell proliferation after anti-CD3 stimulation was similar regardless of the form of co-stimulation. Similarly, B7-1 and B7-2 could both maintain long-term expansion of CD4 cells. The co-stimulatory effects of both B7-1 and B7-2 were dependent on CD28 cross-linking, based on complete inhibition of proliferation by ***CD28*** antibody Fab fragments. Co-stimulation with B7-1 and B7-2 induced high levels of cytokine secretion by resting T cells, and the effects of B7-1 and B7-2 could not be distinguished. This conclusion is based on analysis of the initial activation of CD28+ T cells, as well as T cell subpopulations consisting of CD4+ and CD8+ T cells. Both B7-1 and B7-2 could elicit IL-4 secretion from CD4+ T cells while anti-***CD28*** antibody induced substantially less IL-4 secretion. Furthermore, both B7-1 and B7-2 could stimulate high levels of IFN-gamma and IL-4 from CD4+CD45RO+ cells, while neither B7 receptor could co-stimulate IFN-gamma and IL-4 secretion from CD4+CD45RA+ T cells. B7-1 and B7-2 could, however, co-stimulate CD4+CD45RA+ T cells to secrete IL-2. By contrast, when previously activated T cells were tested, re-stimulation of CD4+ T cell blasts with B7-1 or B7-2 resulted in higher secretion of IL-4 and IL-5 than anti-CD28, while re-stimulation with anti-CD28 antibody maintained a higher level of secretion of IL-2 and IFN-gamma than B7-1 or B7-2. These observations may have important implications because they suggest that the manner of CD28 ligation can be a critical determinant in the development of cytokine secretion that corresponds to T-h1- and T-h2-like patterns of differentiation. Together these observations suggest that there are no intrinsic differences between B7-1 and B7-2 in their ability to co-stimulate the populations of cells that we have tested.

5/7/7 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12713229 BIOSIS NO.: 199598181062
CD28 activation promotes Th2 subset differentiation by human CD4+ cells
AUTHOR: King Christopher L (Reprint); Stupi Robert L; Craighead Nancy; June Carl H; Thyphronitis George
AUTHOR ADDRESS: Div. Geographic Med., Case Western Reserve Univ., 2109 Adelbert Rd., Cleveland, OH 44106-4983, USA**USA
JOURNAL: European Journal of Immunology 25 (2): p587-595 1995 1995
ISSN: 0014-2980
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Ligation of CD28 provides a costimulatory signal to T cells necessary for their activation resulting in increased interleukin (IL)-2 production in vitro, but its role in IL-4 and other cytokine production and functional differentiation of T helper (Th) cells remains uncertain. We studied the pattern of cytokine production by highly purified human adult and neonatal CD4+ T cells activated with anti-CD3, phorbol

12-myristate 13-acetate (PMA) and ionomycin, or phytohemagglutinin (PHA) in the presence or absence of anti-CD28 in repetitive stimulation-rest cycles. Initial stimulation of CD4+ cells with anti-CD3 (or the mitogens PHA or PMA+ionomycin) and anti-CD28 monoclonal antibodies induced IL-4, IL-5 and interferon-gamma (IFN-gamma) production and augmented IL-2 production (6- to 11-fold) compared to cells stimulated with anti- ***CD3*** or mitogen alone. The anti-CD28-induced cytokine production corresponded with augmented IL-4 and IL-5 mRNA levels suggesting increased gene expression and/or mRNA stabilization. Most striking, however, was the progressively enhanced IL-4 and IL-5 production and diminished IL-2 and IFN-gamma production with repetitive consecutive cycles of ***CD28*** stimulation. The enhanced Th2-like response correlated with an increased frequency of IL-4-secreting cells; up to 70% of the cells produced IL-4 on the third round of stimulation compared to only 5% after the first stimulation as determined by ELISPOT. ***CD28*** activation also promoted a Th2 response in naive neonatal CD4+ cells, indicating that Th cells are induced to express a Th2 response rather than preferential expansion of already established Th2-type cells. This ***CD28*** -mediated response was IL-4 independent, since enhanced IL-5 production with repetitive stimulation cycles was not affected in the presence of neutralizing anti-IL-4 antibodies. These results indicate that ***CD28*** activation may play an important role in the differentiation of the Th2 subset in humans.

5/7/8 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12672161 BIOSIS NO.: 199598139994
Distinct signal transduction in mouse CD4+ and CD8+ splenic T cells after CD28 receptor ligation
AUTHOR: Abe Ryo (Reprint); Vandenberghe Peter; Craighead Nancy; Smoot Douglas S; Lee Kelvin P; June Carl H
AUTHOR ADDRESS: Immune Cell Biol. Program, Naval Med. Research Inst., Tissue Bank, Build. 1, Room 159, 8901 Wisconsin Ave., Code 0613, Bethesda, MD 20889, USA**USA
JOURNAL: Journal of Immunology 154 (3): p985-997 1995 1995
ISSN: 0022-1767
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Current evidence suggests that recognition of Ag/MHC by the TCR alone is insufficient to lead to T cell proliferation or effector function. For a Th cell to produce sufficient IL-2 to allow autocrine-driven clonal expansion, there is a requirement for so-called "costimulatory" or "accessory" signals in addition to TCR ligation by Ag/MHC. Although the first signal delivered by TCR ligation has been well characterized, information regarding the biochemical nature of second signals is limited. In the present report, using a newly generated mAb specific for CD28, signal transduction by the CD28 receptor has been studied in mouse splenic T cells. When freshly isolated splenic T cells were assessed, cross-linking of CD28 by mAb did not induce increases in intracellular calcium concentration whereas TCR cross-linking was able to induce calcium mobilization. In contrast, when T cells were activated by phorbol ester treatment or by in vitro culture, CD28 ligation was able to induce calcium mobilization in 60 to 70% of splenic T cells. Unexpectedly, the ***CD28*** -induced calcium response was mainly limited to T cells of the CD4+ subset, whereas both CD4+ and CD8+ T cell subsets showed increases in (Ca-2+)-i of similar magnitude

after ***CD3*** -epsilon ligation. The temporal nature of the ***CD28*** -induced signal was also different from TCR-induced calcium mobilization. CD28-induced signals were delayed in onset and sustained in duration in contrast to TCR signals that had short latency and brief duration. Differential expression of ***CD28*** on the surface of activated CD4+ or CD8+ T cells did not appear to account for the differences in signal transduction between the two T cell subsets. The preferential responsiveness of the CD4+ T cell population to CD28 -induced signaling was also observed in downstream events such as the induction of IL-2R, CD69 expression, and in cellular proliferation. These results indicate that the costimulatory signal delivered by CD28 may have fundamentally different biochemical properties in CD4 and CD8 T cell subsets, and therefore the functional role of CD28 may differ in these T cell subsets.

5/7/9 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11984278 BIOSIS NO.: 199497005563
Rapid activation of c-Raf-1 after stimulation of the T-cell receptor or the muscarinic receptor type 1 in resting T cells
AUTHOR: Siegel Jeffrey N (Reprint); June Carl H; Yamada Hidehiro; Rapp Ulf R; Samelson Lawerence E
AUTHOR ADDRESS: NMRI/ICBP, Mail Stop 6, Bethesda, MD 20889-5607, USA**USA
JOURNAL: Journal of Immunology 151 (8): p4116-4127 1993 1993
ISSN: 0022-1767
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RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The c-Raf-1 serine/threonine kinase is an important component of signal transduction pathways mediating the effects of a variety of growth factors. In activated T cells, IL-2 has been shown to induce activation of c-Raf-1, but c-Raf-1 has not previously been shown to be activated through the T-cell receptor (TCR) in resting G-0 T cells. Using a sensitive immune complex kinase reaction, we show that cross-linking of the stimulatory and costimulatory receptors CD3, CD4, or CD28 induces c-Raf-1 activation in highly purified resting peripheral blood human T cells. In contrast, cross-linking the nonstimulatory receptor CD45 did not induce c-Raf-1. Surprisingly, although earlier studies had shown delayed kinetics in response to Thy-1 stimulation in murine cells, c-Raf-1 activation in response to CD3 cross-linking was one of the earliest measurable events. In spite of its early kinetics, c-Raf-1 activation was found to be downstream of several other early signal transduction events, including activation of a tyrosine kinase and a tyrosine phosphatase. Several lines of evidence suggest that activation of c-Raf-1 in response to TCR stimulation may be PKC-dependent: first, phorbol esters are extremely potent activators of c-Raf-1 in human T cells; second, the kinetics of accumulation of products of phosphatidylinositol hydrolysis coincides with the kinetics of c-Raf-1 activation; and third, physiologic activation of the PLC/PKC pathway through a transfected, G-protein-coupled receptor HM1 induced similar levels of c-Raf-1 activation with a similar time course. We conclude that c-Raf-1 activation is tightly coupled to TCR stimulation and may participate in signal transduction pathways in resting, G-0 T cells. The observation that the HM1 receptor can also activate c-Raf-1 suggests that T cells have the capability to utilize both tyrosine kinase-dependent and tyrosine kinase-independent mechanisms of c-Raf-1 activation.
? s (cd3 or okt3 or anti(W)cd3)(20n)(cd28 or anti(w)cd28)(20n)(immobili?)(20n)(same or together)

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          96835  CD3
          10854  OKT3
        2152013  ANTI
          96835  CD3
          21794  ANTI(W)CD3
          27181  CD28
        2152013  ANTI
          27181  CD28
            4102  ANTI(W)CD28
         312784  IMMOBILI?
        2400213  SAME
         857343  TOGETHER
      S7      58  (CD3 OR OKT3 OR ANTI(W)CD3)(20N)(CD28 OR
                  ANTI(W)CD28)(20N)(IMMOBILI?)(20N)(SAME OR TOGETHER)
? rd s7
      S8      25  RD S7  (unique items)
? s s8 and py<1998
Processing
                25  S8
       46224555  PY<1998
      S9      13  S8 AND PY<1998
? rd s9
     S10      13  RD S9  (unique items)
? t s10/7/all

 10/7/1     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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13351397   BIOSIS NO.: 199698819230
Increase of intracellular calcium is the essential signal for the
  expression of CD40 ligand
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JOURNAL: European Journal of Immunology  26 (4): p846-850 1996 1996
ISSN: 0014-2980
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: CD40 ligand (CD40L) is present on activated but not on resting T
  cells. In contrast to the activation markers CD25 and CD71, a strong
  CD40L expression could be induced by calcium ionophore alone but not by
  phorbol 12-myristate 13-acetate (PMA). Ionomycin induced a very early
  mRNA and protein surface expression of CD40L within the first 2 h,
  whereas CD25 and CD71 did not appear earlier than 6 h after stimulation.
  The mitogens phytohemagglutinin and concanavalin A induced little CD40L,
  but together with PMA, a markedly increased CD40L expression was
  observed. In T cells stimulated with   ***immobilized***     ***anti***  -
  CD3, co-stimulation with anti-CD28 or PMA induced an
  earlier and higher maximal CD40L expression. CD40L expression of purified
  T cells was higher and more prolonged compared to that of T cells in
  unseparated peripheral blood mononuclear cells. We conclude that the
  expression of CD40L on T cells is profoundly different from other early
  activation markers with regard to signal requirements, kinetics and the
  role of accessory cells in the system.


 10/7/2     (Item 2 from file: 5)
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DIALOG(R)File 5:Biosis Previews(R)

12909060 BIOSIS NO.: 199598376893
Costimulatory requirements of naive CD4+ T cells: ICAM-1 or B7-1 can costimulate naive CD4 T cell activation but both are required for optimum response
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JOURNAL: Journal of Immunology 155 (1): p45-57 1995 1995
ISSN: 0022-1767
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Efficient initiation of a CD4 T cell response requires both activation through the TCR and costimulation provided by molecules on APC with counterreceptors on the T cell. We investigated the relative contribution of the ICAM-1:LFA-1 and B7:CD28/CTLA-4 costimulatory pathways in naive T cell activation, using either anti-CD28 Ab or fibroblast cell lines transfected with I-E-k which express either no costimulatory molecules, ICAM-1 alone, B7-1 alone, or ICAM-1 and B7-1 ***together*** . Peptide Ag or ***immobilized*** ***anti*** - ***CD3*** was used to provide the TCR signal. CD4 T cells from mice transgenic for the V-beta-3/V-alpha-11 TCR, which recognize a peptide of pigeon cytochrome c complexed to I-E-k were used as a source of naive T cells. Naive T cells stimulated with Ag or anti-CD3 responded well to high numbers of APC expressing either ICAM-1 alone or B7-1 alone. However, APC expressing both ICAM-1 and B7-1 were much better stimulators of proliferation and IL-2 secretion at low cell numbers, and were far superior inducers of IL-2 at higher numbers, indicating a synergy between the two pathways. Stimulation provided by ICAM-1 could not be solely attributed to adhesive strengthening of other pathways, since costimulation was seen when immobilized anti-CD3 was used and when ICAM-1 only APC were added, indicating that ICAM-1 was in fact acting as a classic costimulatory molecule. Both the magnitude of the response and the amount of costimulation required for response were dependent on the intensity of TCR interaction. These results suggest that an efficient naive T cell response requires both a strong TCR signal and more than one costimulatory signal that will synergize with the TCR signal. This offers an explanation as to why APC such as dendritic cells and activated B cells, which express high levels of multiple costimulatory/adhesion molecules, are the only APC that elicit naive T cell responses.

10/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12338299 BIOSIS NO.: 199497359584
Induction of anergy in resting human T lymphocytes by immobilized anti-CD3 antibodies
AUTHOR: Wolf Hans (Reprint); Muller Yvonne; Salmen Sibylle; Wilmanns Wolfgang; Jung Gundram
AUTHOR ADDRESS: Klinische Haematologie, Marchioninistr. 25, D-81377 Muenchen, Germany**Germany
JOURNAL: European Journal of Immunology 24 (6): p1410-1417 1994 1994
ISSN: 0014-2980
DOCUMENT TYPE: Article

RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: How the T cell receptor(TcR)/CD3 complex mediates not only the induction of T cell activation but also suppressive effects like T cell anergy or apoptosis is not well understood. Here we describe a series of preincubation and restimulation experiments which demonstrate that primary stimulation of resting, unseparated human T cells with mitogenic doses of immobilized anti-CD3 antibodies induces hyporesponsiveness upon restimulation of the cells.Various costimuli can prevent this type of anergy to a variable degree if present during the preincubation period, phorbol 12-myristate 13-acetate (PMA) being the most and anti-CD4 antibody the least effective. If employed together with anti-CD3 antibody during the restimulation phase of the assay, interleukin (IL)-2, IL-4 and anti-CD28 antibody break anergy almost completely. Proliferation induced by a submitogenic dose of anti-CD3 antibody supplemented by costimulatory signals (anti-CD2, anti-CD4, anti-CD28, IL-2, IL-4 or PMA) does Dot result in hyporesponsiveness. Taken together, these results support a modified view of the two-signal model for T cell activation according to which anergy induction in resting T cells occurs if primary proliferation is induced by high density triggering of the TcR/CD3 complex in the absence of accessory signals.We discuss possible implications of these findings for the induction of peripheral tolerance.

10/7/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12163447 BIOSIS NO.: 199497184732
Helper effector function of human T cells stimulated by anti-CD3 mAb can be enhanced by co-stimulatory signals and is partially dependent on CD40-CD40 ligand interaction
AUTHOR: Kwekkeboom Jaap; De Rijk Diana; Karsan Ahmad; Barcy Serge; De Groot Cornelis; De Boer Mark (Reprint)
AUTHOR ADDRESS: Lab. Cell Biol. Histol., Cellular Immunol. Group, Univ. Amsterdam, Academic Med. Center, Meibergdreef 15, NL-1105 AZ Amsterdam, Netherlands**Netherlands
JOURNAL: European Journal of Immunology 24 (3): p508-517 1994 1994
ISSN: 0014-2980
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: In this study we have investigated whether anti-CD3-induced human T cell help for immunoglobulin production could be enhanced by co-stimulation of the T cells via other T cell surface molecules, and the contribution of CD40-CD40 ligand interaction to the execution of T helper effector function induced by these different stimulatory signals. In a system in which irradiated tonsillar T cells were stimulated with immobilized anti-CD3 monoclonal antibody (mAb), it was found that ligation of CD2 with a mitogenic pair of mAb considerably enhanced ***anti*** - ***CD3*** -induced T cell help for immunoglobulin production. Likewise, ligation of CD28 with mAb enhanced T helper activity, although to a lesser extent. Upon addition of ***anti*** - ***CD28*** and anti-CD2 mAb together, an even higher immunoglobulin production was observed. This combination resulted in a four- to fivefold increase in immunoglobulin production as compared to cultures in which T cells were stimulated with ***anti*** - ***CD3*** mAb alone. The effect of ligation with B7, the natural ligand of CD28, was studied in a system which utilizes the

presentation of anti-CD3 mAb on human Fc-gamma-RII-expressing mouse fibroblasts which were co-transfected with human B7. It appeared that B7 could stimulate help for immunoglobulin production much more efficiently than ligation of ***CD28*** with mAb did. Physical separation of B cells from T cells led to complete abrogation of immunoglobulin production. Blocking of CD40 with specific mAb, which have no intrinsic B cell stimulatory properties, or the CD40 ligand with a soluble CD40-human IgM fusion protein, resulted in dose-dependent, but only partial, inhibition of T cell-dependent immunoglobulin production with all modes of T cell activation tested. A clear correlation was found between the induction of CD40 ligand expression on the T cells by the different modes of co-stimulation and subsequent immunoglobulin production by the B cells. It is concluded that ligation of CD28 and/or CTLA-4, and of CD2 can generate co-stimulatory signals for T cell help for immunoglobulin production, which was found to be only partially dependent on the CD40-CD40 ligand interaction.

10/7/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11984274 BIOSIS NO.: 199497005559
Co-stimulatory signal delivered by CD73 molecule to human CD45RA-hiCD45RO-lo (naive) CD8+ T lymphocytes
AUTHOR: Dianzani Umberto (Reprint); Redoglia Valter; Bragardo Manuela; Attisano Carmela; Bianchi Alberto; Di Franco Daniela; Ramenghi Ugo; Wolff Henrik; Thompson Linda F
AUTHOR ADDRESS: Dip. Medicina ed Oncologia Sperimentale, Sezione Ematologia, Universita' di Torino, via Genova 3, 10138 Torino, Italy** Italy
JOURNAL: Journal of Immunology 151 (8): p3961-3970 1993 1993
ISSN: 0022-1767
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: CD73 is a molecule expressed by a subset of CD8+ human T lymphocytes and is involved in T cell activation. CD73 expression and function were analyzed in peripheral blood CD45RA-hiCD45RO-lo (naive) and CD45RA-loCD45RO-hi (memory) CD8+ cells. We found that CD73 was expressed by a majority of naive cells (74 +- 12%), whereas fewer memory cells were CD73+(29 +- 10%). Moreover, CD73 was selectively expressed by the CD11b- subset of naive CD8+ cells, which were almost all CD73+. The ***same*** result was found on CD8+ cord blood lymphocytes, which prevalently display the naive phenotype. Naive CD8+CD11b- cells were almost unresponsive to CD3 engagement, but this apparent anergy was completely overcome when CD3 and CD73 were simultaneously cross-linked by plastic-immobilized CD73 and CD3 mAb, showing that CD73 delivers an accessory signal that allows their activation via the ***CD3*** /TCR. This costimulatory signal was tenfold more potent than that induced by ***CD28*** ligation. A phosphotyrosine analysis by Western blotting showed that cross-linking of CD73 induced the phosphorylation of two proteins with a molecular mass of apprx 28 and 100 kda respectively, whereas ligation of CD3 induced phosphorylation of many subtrates. When ***CD3*** and CD73 were simultaneously triggered these substrates were hypophosphorylated. Because CD73 is linked to the cell surface by a GPI anchor, the transduction of this signal is probably mediated by a lateral interaction with transmembrane molecules. This hypothesis was assessed by cocapping, which showed that CD73 associates strongly with CD45RC, moderately with CD8, and weakly with CD3. These

data suggest that CD73 signaling is coupled to both tyrosine kinase and phosphatase activities.

10/7/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10681075 BIOSIS NO.: 199191063966
ACTIVATION AND EXPANSION OF TUMOR-INFILTRATING LYMPHOCYTES BY ANTI-CD3 AND ANTI-CD28 MONOCLONAL ANTIBODIES
AUTHOR: NIJHUIS E W P (Reprint); V D WIEL-VAN KEMENADE E; FIGDOR C G; VAN LIER R A W
AUTHOR ADDRESS: CENTRAL LAB NETH RED CROSS BLOOD TRANSFUSION SERV, PO BOX 9406, 1006 AK AMSTERDAM, NETH**NETHERLANDS
JOURNAL: Cancer Immunology Immunotherapy 32 (4): p245-250 1990
ISSN: 0340-7004
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Cytotoxic T lymphocytes from healthy donors can be expanded to high numbers from the peripheral blood using combinations of anti-***CD3*** and ***anti*** - ***CD28*** monoclonal antibodies (mAb). We investigated whether these antibodies could also be used to induce outgrowth of tumour-infiltrating lymphocytes (TIL) from tumour tissue. In the initiation phase of TIL culture immobilized anti-CD3 antibodies together with anti-CD28 mAb and low-dose interleukin-2 induced a rapid expansion of T cells from various human tumour tissues. The cultured cells showed high levels of cytotoxic T lymphocyte activity, but low levels of lymphokine-activated killer cell activity were generated. This study shows that TIL can be efficiently expanded from tumour tissue by combinations of anti-CD3 and ***anti*** - ***CD28*** antibodies. This protocol for cell expansion in vitro may substantially reduce the time required to reach sufficient numbers of TIL for re-infusion to the patient.

10/7/7 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10187054 BIOSIS NO.: 199089104945
CD28 IS AN INDUCIBLE T CELL SURFACE ANTIGEN THAT TRANSDUCES A PROLIFERATIVE SIGNAL IN CD3-POSITIVE MATURE THYMOCYTES
AUTHOR: TURKA L A (Reprint); LEDBETTER J A; LEE K; JUNE C H; THOMPSON C B
AUTHOR ADDRESS: MSRB-II, ROOM 1560, 1150 WEST MEDICAL CENTER DR, UNIV MICH MED CENT, ANN ARBOR, MI 48109-0676, USA**USA
JOURNAL: Journal of Immunology 144 (5): p1646-1653 1990
ISSN: 0022-1767
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The rearrangement of TCR genes during thymic ontogeny creates a repertoire of T cell specificities that is refined to ensure the deletion of autoreactive clones and the MHC restriction of T cell responses. Signals delivered via the accessory molecules CD2, CD4, and CD8 have a crucial role in this phase of T cell differentiation. Recently, CD28 has been identified as a signal transducing molecule on the surface of most mature T cells. Perturbation of the CD28 molecule stimulates a novel

pathway of T cell activation regulating the production of a variety of lymphokines including IL-2. We have studied the expression and function of ***CD28*** during thymic ontogeny, and in resting and activated PBL. A variable percentage of resting thymocytes were CD28+ (3 to 25%, n = 8), but it was found in high density only on mature CD3+(bright) CD4/CD8 cells. Both unseparated thymocytes and isolated CD3-CD28-/dull cells proliferated when stimulated with PMA plus IL-2 or PMA plus ionomycin. PMA treatment also rapidly up-regulated CD28 expression in the CD3- subset as these cells became CD3-CD28+(bright). Despite the ability of PMA to induce high density CD28 expression in CD3- cells, CD3- thymocytes did not proliferate in response to PMA plus anti-CD28 mAb, in contrast to unseparated cells. CD3+ thymocytes stimulated with immobilized anti-CD3 mAb also failed to proliferate in culture. However, the addition of either IL-2 or anti-CD28 mAb supported proliferation, suggesting that only CD3+ cells could respond to CD28 signaling. The comitogenic effect of anti-CD3 and anti-CD28 mAb was IL-2 dependent as it was abrogated by an anti-IL-2R mAb. Interestingly, the expression of CD28 on the cell surface of CD3+ cells was also inducible, as flow cytometric analysis demonstrated a 10-fold increase in cell surface CD28 by 24 to 48 h after anti-CD3 stimulation of both ***CD3*** + thymocytes and peripheral blood T cells. This increase was accounted for by a commensurate increase in ***CD28*** mRNA levels. Together, these results suggest that CD28 is an inducible T cell antigen in both ***CD3*** - and ***CD3*** + cells. In addition, stimulation of the CD28 pathway can provide a second signal to support the growth of CD3+ thymocytes stimulated through the TCR/CD3 complex, and may therefore represent a mechanism for positive selection during thymic ontogeny.

09590012 BIOSIS NO.: 198987037903
CD45 REGULATES SIGNAL TRANSDUCTION AND LYMPHOCYTE ACTIVATION BY SPECIFIC ASSOCIATION WITH RECEPTOR MOLECULES ON T OR B CELLS
AUTHOR: LEDBETTER J A (Reprint); TONKS N K; FISCHER E H; CLARK E A
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JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 85 (22): p8628-8632 1988
ISSN: 0027-8424
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Evidence is presented that the leukocyte common antigen CD45 can regulate both signal transduction by lymphocyte receptor molecules and T- and B-cell proliferation in a manner dependent on specific interactions between these receptors on the cell surface. Formation of homoaggregates of CD3, CD2, and CD28 on the surface T cells induced by crosslinking with monoclonal antibodies (mAbs) results in an increase in cytoplasmic free calcium concentration ([Ca2+]i). This increase in [Ca2+]i was abolished when these receptors were crosslinked to CD45 on the cell surface. In contrast, the increase in [Ca2+]i induced by formation of homoaggregates of CD4 was strongly amplified when CD4 was coupled to CD45. T-cell proliferation initiated by immobilized anti-CD3 was inhibited by anti-CD45 or anti-CD45R when immobilized on the ***same*** surface, but not when in solution. Similarly, proliferation after stimulation of the CD2 and CD28 receptors was inhibited when a CD45 mAb was crosslinked to either CD2 or CD28 mAbs, but not when

a CD45-specific mAb was bound to the cell surface separately. In B cells, the increase in [Ca2+]i and resulting proliferation induced by crosslinking either the CD19 or Bgp95 receptors was inhibited by coupling these molecules to CD45. Thus, CD45 appears to modify other cellular receptors functionally when brought into close physical association with them. The homology of the CD45 conserved cytoplasmic domains with a major human placental protein tyrosine here result from alterations in the phosphorylation state of tyrosyl residues in membrane-associated proteins.

0076905113 EMBASE No: 1997198230

Use of the methylxanthine derivative A802715 in transplantation immunology: I. Strong in vitro inhibitory effects on CD28-costimulated T cell activities

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Transplantation (TRANSPLANTATION) (United States) June 27, 1997, 63/12 (1813-1818)
CODEN: TRPLA ISSN: 0041-1337
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 39

Background. Recently, methylxanthines such as pentoxifylline (PTX) were shown to be immunosuppressive in vitro. Unfortunately, when used in transplant patients, PTX was poorly active as an immunosuppressant. Here we report that the new methylxanthine derivative A802715 not only is more active than PTX, it also suppresses the cyclosporine (CsA)-resistant 'signal two'- dependent pathway oft cell proliferation, making it an interesting drug to associate with CsA. Methods. 'Signal one'- and 'signal two'-dependent T cell activation was investigated with purified human T cells stimulated with immobilized anti-CD3 or anti-CD28 monoclonal antibody (mAb) plus phorbol myristate acetate (PMA) or with a 3T6 mouse fibroblast cell line presenting anti-CD3 mAb on transfected human Fcgamma receptors II (FcgammaRII) in the presence or absence of transfected B7-1 (CD80) molecules. Results. A802715 was more immunosuppressive in the mixed lymphocyte reaction (MLR) than PTX. A802715 dose-dependently suppressed polyclonal signal one-dependent T cell activation induced by ***anti*** - ***CD3*** mAb/PMA. In addition, A802715 also suppressed signal two- dependent T cell proliferation induced by ***anti*** - ***CD28*** mAb/PMA. The expression of the interleukin-2 receptor on T cells stimulated by anti-CD3 mAb presented on 3T6fFcgammaRII cells was equally well suppressed by A802715 and PTX. In contrast, interleukin-2 receptor or CD40L (gp39) expression by T cells after stimulation with the same anti-CD3 mAb- 3T6/FcgammaRII cells, but coexpressing transfected B7-1, was only suppressed by A802715. The anticipated synergism between A802715 and CsA was confirmed in MLR assays. Moreover, generation of cytotoxic T lymphocytes during MLR with Epstein-Barr virus-transformed B cells, which strongly express B7-1 and B7-2, was also inhibited by A802715. Conclusions. These in vitro data

indicate that the A802715 (1) is a stronger immunosuppressant for T cells than PTX, (2) suppresses T cell activation pathways that are resistant to PTX or CsA, and (3) acts synergistically with CsA.

10/7/10 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

0075180455 EMBASE No: 1992332146
Inhibition of anti-CD3 monoclonal antibody-induced T-cell proliferation by dexamethosone, isoproterenol, or prostaglandin E SUB 2 either alone or in combination
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Cellular and Molecular Neurobiology (CELL. MOL. NEUROBIOL.) (United States) November 16, 1992, 12/5 (411-427)
CODEN: CMNED ISSN: 0272-4340
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English

1. The purpose of these studies was to investigate the modulation of the proliferation of human T cells obtained from peripheral blood by dexamethosone (DEX), isoproterenol (ISO), and prostaglandin E SUB 2 (PGE SUB 2). The former two substances interact with T cells via the glucocorticoid and beta- adrenergic receptors respectively. When occupied by their natural ligands, glucocorticosteroids and catecholamines, these receptors have a role in modulating T-cell function during stress. During the inflammatory response increased levels of PGE SUB 2 bind to their receptors on T cells and thus alter responsiveness. Proliferation of T cells was induced by immobilized anti-CD3 monoclonal antibody (mAb) in the presence or absence of an additional costimulatory signal delivered by ***anti*** - ***CD28*** mAb. 2. Various physiologic concentrations of DEX, ISO, or PGE SUB 2 were added at the time of initiation of the cultures and subsequent proliferation of the unstimulated T cells was determined. The results demonstrate that physiologic concentrations of all three of these agents inhibit the anti-***CD3*** mAb-induced proliferation of T cells. 3. Although DEX and PGE SUB 2 were equipotent in suppressing T-cell proliferation, ISO was much less effective. 4. Because concomitant elevations in the peripheral levels of these substances may occur, experiments were performed to determine the T-cell inhibitory effects of DEX together with either PGE SUB 2 or ISO. Synergistic suppression of T-cell proliferation was observed when various concentrations of DEX and PGE SUB 2, but not DEX and ISO, were added to cultures. This synergistic suppression could not be explained by an increase in cAMP accumulation in T cells stimulated with DEX and PGE SUB 2. 5. Finally, the addition of anti-CD28 mAb to anti-CD3 mAb-stimulated T cells overcame much of the suppression of proliferation induced by PGE SUB 2 or ISO but less so than that induced by DEX.

10/7/11 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12682523 PMID: 9550389
Effects of CD28 costimulation on long-term proliferation of CD4+ T cells

in the absence of exogenous feeder cells.
Levine B L; Bernstein W B; Connors M; Craighead N; Lindsten T; Thompson C B; June C H
Henry M. Jackson Foundation for the Advancement of Military Medicine, U.S. Military HIV Research Program, Bethesda, MD 20889, USA.
Journal of immunology (Baltimore, Md. - 1950) (UNITED STATES) Dec 15 1997, 159 (12) p5921-30, ISSN 0022-1767--Print Journal Code: 2985117R
Publishing Model Print
Document type: Journal Article; Research Support, U.S. Gov't, Non-P.H.S.
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
In this report, conditions for prolonged in vitro proliferation of polyclonal adult CD4+ T cells via stimulation with immobilized anti-CD3 plus anti-CD28 have been established. CD4+ cells maintained exponential growth for more than 60 days during which a total 10(9)- to 10(11)-fold expansion occurred. Cell cultures exhibited cyclical changes in cell volume, indicating that, in terms of proliferative rate, cells do not have to rest before restimulation. Indeed, electronic cell size analysis was the most reliable method to determine when to restimulate with additional ***immobilized*** mAb. The initial approximately 10(5)-fold expansion was autocrine, occurring in the absence of exogenous cytokines or feeder cells. Addition of recombinant human IL-2 after the initial autocrine expansion resulted in continued exponential proliferation. Phorbol ester plus ionomycin also induced long-term growth when combined with anti-***CD28*** stimulation. Analysis of the T cell repertoire after prolonged expansion revealed a diverse repertoire as assessed by anti-TCR Vbeta Abs or a PCR-based assay. Cytokines produced were consistent with maintenance of both Th1 and Th2 phenotypes; however, the mode of CD3 and ***CD28*** stimulation could influence the cytokine secretion pattern. When anti-CD3 and anti-CD28 were immobilized on the same surface, ELISAs on culture supernatants revealed a pattern consistent with Th1 secretion. Northern analysis revealed that cytokine gene expression remained inducible. Spontaneous growth or cell transformation was not observed in more than 100 experiments. Together , these observations may have implications for gene therapy and adoptive immunotherapy. Furthermore, these culture conditions establish a model to study the finite lifespan of mature T lymphocytes.
Record Date Created: 19980423
Record Date Completed: 19980423

10/7/12 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12682223 PMID: 9548474
T cell stimulation via CD47: agonistic and antagonistic effects of CD47 monoclonal antibody 1/1A4.
Waclavicek M; Majdic O; Stulnig T; Berger M; Baumruker T; Knapp W; Pickl W F
Institute of Immunology, University of Vienna, Austria.
Journal of immunology (Baltimore, Md. - 1950) (UNITED STATES) Dec 1 1997, 159 (11) p5345-54, ISSN 0022-1767--Print Journal Code: 2985117R
Publishing Model Print
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
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CD47/integrin-associated protein has been extensively studied on various cell types. The function of CD47 on T cells, however, remained poorly understood. We demonstrate here that our CD47 mAb 1/1A4 has both inhibitory as well as costimulatory effects in terms of T cell activation. Soluble, not cross-linked, CD47 mAb 1/1A4 blocks allogeneic MLRs. This effect is predominantly observed with suboptimal numbers of stimulator cells. In contrast, cross-linking of CD47 in the presence of CD28 mAb or phorbol ester induces vigorous T cell proliferation that is sensitive to cyclosporin A. Cross-linking, but not ***immobilization*** , of the CD47 mAb 1/1A4 is an essential requirement for the CD28 - or phorbol ester-dependent induction of T cell mitogenesis. Furthermore, CD47 mAb 1/1A4 induces T cell proliferation when coimmobilized with a CD3 mAb to the ***same*** surface. Ligation with cross-linked 1/1A4 mAb induces an increase in intracellular free calcium levels and leads to tyrosine phosphorylation of various cellular proteins and, in the presence of suboptimal concentrations of plate-bound CD3 mAb, to enhanced IL-2 promotor activity in T cells. Furthermore, we present evidence that upon cross-linking of CD47 with mAb 1/1A4, purified T cells acquire responsiveness for several T cell growth factors. IL-1beta and/or IL-6 dramatically augment this CD47-induced cytokine responsiveness. Our results suggest that the novel activation pathway via CD47 might be critically involved in Ag-dependent and Ag-independent T cell functions.

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Inhibition of anti-CD3 monoclonal antibody-induced T-cell proliferation by dexamethasone, isoproterenol, or prostaglandin E2 either alone or in combination.

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1. The purpose of these studies was to investigate the modulation of the proliferation of human T cells obtained from peripheral blood by dexamethasone (DEX), isoproterenol (ISO), and prostaglandin E2 (PGE2). The former two substances interact with T cells via the glucocorticoid and beta-adrenergic receptors respectively. When occupied by their natural ligands, glucocorticosteroids and catecholamines, these receptors have a role in modulating T-cell function during stress. During the inflammatory response increased levels of PGE2 bind to their receptors on T cells and thus alter responsiveness. Proliferation of T cells was induced by immobilized anti-CD3 monoclonal antibody (mAb) in the presence or absence of an additional costimulatory signal delivered by ***anti*** - ***CD28*** mAb. 2. Various physiologic concentrations of DEX, ISO, or PGE2 were added at the time of initiation of the cultures and subsequent proliferation of the unstimulated T cells was determined. The

results demonstrate that physiologic concentrations of all three of these agents inhibit the anti-CD3 mAb-induced proliferation of T cells. 3. Although DEX and PGE2 were equipotent in suppressing T-cell proliferation, ISO was much less effective. 4. Because concomitant elevations in the peripheral levels of these substances may occur, experiments were performed to determine the T-cell inhibitory effects of DEX ***together*** with either PGE2 or ISO. Synergistic suppression of T-cell proliferation was observed when various concentrations of DEX and PGE2, but not DEX and ISO, were added to cultures. This synergistic suppression could not be explained by an increase in cAMP accumulation in T cells stimulated with DEX and PGE2. 5. Finally, the addition of anti-CD28 mAb to anti-CD3 mAb-stimulated T cells overcame much of the suppression of proliferation induced by PGE2 or ISO but less so than that induced by DEX.

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